Finally, it is intriguing to wonder whether the excellent correlation between plasma C reactive protein concentrations and disease activity reflects not just the acute phase response to the original underlying pathological process, but also the capacity of C reactive protein to exacerbate existing tissue damage: possibly the more C reactive protein you produce, the sicker you get.

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"Normal" blood glucose and coronary risk

Dose response effect seems consistent throughout the glycaemic continuum

Although diabetes is a strong risk factor for coronary heart disease, the association between glycaemia within the "normal range" and coronary heart disease has been somewhat controversial.[1] A 1979 collaborative report from 15 countries found the risk ratio in the highest versus the lowest centile of glycaemia to range from 0.34 to 6.07 in men from Finland, Denmark, France, the United Kingdom, and the United States.[2] In other cohort studies, including Whitehall[3] and Framingham,[4] there appeared to be a threshold effect, with risk observed only at glucose levels approaching or including current diagnostic criteria for diabetes. There are several possible reasons for these contradictory results, including: the failure to exclude people with diabetes from the cohorts, compatible with a threshold effect; the multifactorial aetiology of coronary heart disease, compatible with confounding; or the large intra-individual variation in glucose (especially postchallenge glucose) values, compatible with misclassification bias.

Glycosylated haemoglobin, an integrated estimate of glucose over the preceding 6-12 weeks, provides a more reliable estimate of usual glycaemia, and should, therefore, be a more precise predictor of coronary heart disease risk. An elegant study by Khaw et al in this issue shows that glycosylated haemoglobin levels are positively associated with the risk of future coronary heart disease in a linear stepwise fashion, with no evidence of a threshold effect and independent of other common risk factors for coronary heart disease (p 15).[5] These are the most convincing data available that the association between glucose and coronary heart disease occurs throughout the normal range of glucose.

Shifting the curve

The finding is important. An association between glycaemia and coronary heart disease in people who do not meet current criteria for a diagnosis of diabetes implies that glucose control for coronary heart disease prevention should begin in those with impaired glucose tolerance, and, as the authors note, points to the desirability of shifting the entire population glycaemia curve to the left. All modifiable risk factors that are continuous variables blur the line between treatment and prevention and lead to the selection of candidates for intervention on feasible and affordable rather than optimal grounds.

There is as yet no trial evidence that improved glucose control will reduce the risk of coronary heart disease among people without diabetes. Even in those with diabetes, the benefits have not been dramatic. In the 1960s the University Group Diabetes Program (UGDP) found a (still unexplained) increased cardiovascular risk in the group treated with tolbutamide, and no difference in cardiovascular disease outcomes between groups assigned to placebo, insulin standard (designed to have little or no effect on glycaemia), or insulin variable (which reduced glucose levels to 7-8 mmol/l).[6] In a study of young people with type 1 diabetes, the Diabetes Control and Complications Trial (DCCT), there were few cardiovascular events and the (non-significant) 40% reduced rate could have been due to chance.[7] The United Kingdom Prevention of Diabetes Study (UKPDS) of older adults

with type 2 diabetes found no significantly reduced risk of cardiovascular disease in the more intensively treated group, who achieved a glycosylated haemoglobin of 7% compared with the control group (glycosylated haemoglobin 7-9%). All the significant benefit was due to a 25% risk reduction in microvascular disease.[8]

Association with microvascular disease

Thus, glycaemia in observational studies and in clinical trials is much more strongly associated with microvascular disease than with coronary heart disease. Is this weaker association because better glucose control is necessary for preventing coronary heart disease than for preventing retinal or renal disease, or because glycaemia is a marker for other risk factors of coronary heart disease more directly in the causal pathway to coronary heart disease? In 1985 Epstein reported an association between glycaemia and coronary heart disease that was independent of cholesterol, blood pressure, and cigarette smoking in five of 13 cohort studies but not in any of the few studies that included women.[9] The paper by Khaw et al does not describe the association in women in their cohort, apparently because there were too few events for meaningful analysis.

Although the evidence that glucose control prevents coronary heart disease is equivocal in patients with diabetes, the trials showing the benefit of lowering cholesterol and blood pressure are quite convincing. In several lipid intervention trials the coronary heart disease risk reduction was similar for those with and without diabetes (about 35%), and the absolute risk reduction was substantially greater in those with diabetes—reflecting their higher coronary heart disease rates.[10] In the UKPDS, blood pressure treatment was much more effective than treatment of glucose in reducing cardiovascular risk,[11] and other antihypertensive trials that included patients with diabetes suggest similar benefits.[12]

Does it matter whether glucose is a causal risk factor or merely a marker for other risk factors? Only if preoccupation with glucose control, of unquestionable value to reduce the risk of retinal and renal disease, obscures the necessity of also aggressively treating hyperlipidemia and hypertension to prevent coronary heart disease.

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Correction

Age related macular degeneration

At a late stage in the publication process we inadvertently introduced an authorship error into this editorial by Neil M Bressler (9 December, pp 1425-7). The published article was attributed to two authors—Professor Bressler and a Professor James P Gills. In fact, Professor Bressler is the sole author, and he is the James P Gills professor of ophthalmology. We apologise for the confusion.